REMARKS/ARGUMENTS

Status of the Claims

Claim 17 has been amended to recite "heparin or other proteoglycan" to provide proper antecedent basis for this term in dependent claim 18. Support for this amendment also resides throughout the specification and in original claims 14, 18, 19, and 51. No new matter is added by way of claim amendment.

The specification and drawings have been amended to address objections raised in the Office Action. No new matter is added by way of these amendments.

Applicant notes that the objection to Applicant's claim to the benefit of provisional application 60/213,504 has been withdrawn.

Claims 1-82 are now pending in this application. Reconsideration of the claims is respectfully requested in view of the foregoing amendments and the following remarks. The comments in the Final Office Action are addressed below in the order set forth therein.

Objection to the Drawings

The Examiner has objected to the drawings as not complying with 37 C.F.R. §1.84(p)(5). Responsive to the Examiner's objection, Applicant submits herewith replacement sheets for those drawings subject to this objection. Accordingly, the specification has been amended in the section pertaining to the Brief Description of the Drawings to reflect these amendments to the drawings. No new matter has been added by way of these amendments. The Examiner is respectfully requested to replace the originally filed sheets for Figures 10, 11, and 14 with the replacement sheets filed concurrently herewith, and to enter the corresponding amendments to the specification.

In view of the submission of replacement sheets for Figures 10, 11, and 14, the objection to the drawings is obviated and should be withdrawn.

Objection to the Specification

The objection to the specification for containing embedded hyperlinks has been maintained. Responsive to the Examiner's objection, the specification has been amended to

remove the "http://www" required to embed the link. The objection is therefore obviated and should be withdrawn.

Objection to the Claims

The objection to claims 1-82 has been maintained on the basis that they recite non-elected species, specifically on the ground that the claims recite "different proteoglycans." As an initial matter, Applicant notes that only claims 14, 15, 16, 17, 18, 19, and 51 recite, or depend from a claim that recites, the term "proteoglycan." Thus, the objection should be withdrawn as to the other pending claims.

Further, there are no rejections under any statutory provision maintained against any of the presently pending claims. All such rejections were withdrawn after Applicant's previous response. Accordingly, Applicant submits that the subgeneric claims drawn to heparin and other proteoglycan will be deemed allowable as they pertain to heparin pending resolution of the double-patenting rejection, at which time Applicant will be entitled to examination of the non-elected species, i.e., other proteoglycan. Accordingly, Applicant elects to withhold amendments to the subgeneric claims of this application until the issue regarding allowability of the subgeneric claims has been resolved.

Rejection under the Judicially Created Doctrine of Obviousness-type Double Patenting

The rejection of claims 1-82 has been maintained under the judicially created doctrine of obviousness-type double patenting over United States Patent No. 6,440,934 (the "'934 patent") in light of Moyer *et al.* (1998) *Exp. Opin. Ther. Patents* 8:1425-1446. Applicant respectfully traverses.

In assessing obviousness-type double patenting, the analysis parallels the analysis for a 35 U.S.C. §103(a) rejection, with the exception that the patent serving as the basis for the double-patenting rejection is not considered prior art. MPEP 804.II.B.1, *citing In re Braithwaite*, 379 F.2d 594 (CCPA 1967). It is the Office's burden to establish obviousness without reliance upon hindsight or the Applicant's own disclosure. In the preceding amendment, Applicant noted that the Office had not carried this burden for the following reasons.

- There was no motivation to modify either Moyer *et al.* or the claimed subject matter of the '934 patent, or to combine the teachings of Moyer *et al.* with the subject matter of the '934 claims, to arrive at Applicant's presently claimed invention.
- Even if such motivation were to exist, Moyer *et al.* and the claimed subject matter of the '934 patent do not provide to one of skill in the art a reasonable expectation of success.
- The '934 claims and Moyer *et al.* fail to teach or suggest all of the limitations set forth in the pending claims of the current application. In particular, peripheral artery disease (PAD) and coronary artery disease (CAD) are separate and distinct clinical conditions, with discrete symptoms and treatments. The successful treatment of one does not provide a reasonable expectation of success for treating the other, particularly when different treatment regimens are being used.

The current Office Action presents several arguments in reply. In the following pages, these arguments are addressed by the paragraph in which they occur in the Office Action.

Paragraph 14.

The Office Action argues that, based upon the results of several animal models referred to in Moyer *et al.*, Moyer *et al.* provide both the motivation to combine these two references and a reasonable chance of success. Specifically, the Office Action states that "FGF-2 was known for its therapeutic value in peripheral artery disease at the time of the invention as evident from Moyer *et al.*" However, Applicant's representative has carefully reviewed Moyer *et al.* and cannot determine where the reference states that "FGF-2 was known for its therapeutic value in peripheral artery disease." Applicant submits that it is only with the benefit of hindsight, based upon data such as that produced in Applicant's phase II clinical trials, that one would conclude that FGF is a known therapeutic for peripheral artery disease. Applicant submits that the rejection is improperly based upon hindsight revision regarding the animal studies reviewed in Moyer *et al.*

Further, Moyer *et al.* reached a far less certain conclusion regarding the efficacy of bFGF than the conclusion alleged in the present Office Action. In particular, Moyer *et al.* cautiously concluded only that "[t]his review provides a strong scientific rationale for the use of bFGF as a *potential* therapeutic agent for the treatment of ischaemic stroke and peripheral vascular disease."

Id. at 1437 (emphasis added). While such a conclusion regarding the *potential* of FGF is evidence that scientific curiosity would be piqued regarding the *possibility* of using bFGF for treating perfusion related disorders, it does not rise to the level of establishing motivation or reasonable expectation of success required for a *prima facie* case of obviousness. At best, the conclusions of Moyer *et al.* may support an obvious-to-try rationale, but this is not the proper standard under Section 103. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Accordingly, the rejection should be withdrawn.

Paragraphs 15 and 16.

With respect to the differences between PAD and CAD, the present Office Action also states: "Regardless of the differences between CAD and PAD, it has been established by the courts that a product inherently possesses characteristics of that product (i.e. including the amino acid sequence of a protein)." *See* paragraph 15 of the Office Action. The Office Action also makes several assertions related to product-by-process claims, and states that "courts have held that when the prior art product reasonable [sic] appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference...." *See* paragraph 16 of the Office Action. Based upon the reasoning of paragraphs 15 and 16, the Office Action concludes that "the administration of FGF to a patient will in fact be sufficient to treat both PAD and CAD due to the inherent salubrious effects of FGF on arterial-related diseases and conditions." The Office Action reasons that, because claims 19 and 20 of the '934 patent include clinical endpoints, one of skill in the art would have substituted the clinical endpoints described in Regensteiner *et al.* (1990) *J. Vascular Med. and Biol.* 2:142-52 and Santilli and Santilli (1999) *Am. Family Physician* 59:1899-1908 to arrive at the methods of the present application. *See* paragraph 17 of the Office Action.

As an initial matter, Applicant notes that the claims of the present application, as well as those of the '934 patent, are *method* claims. Applicant does not claim FGF (or any product, for

that matter). Thus, the standard set forth by the Office Action is not applicable to the claims at issue here.

Moreover, speculation regarding the inherent benefits of FGF cannot substitute for proper evidence on the issues of motivation to combine and reasonable chance of success, which are lacking from the present record. The Federal Circuit has held that "a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 9 F.3d 1531 (Fed. Cir. 1993). Applicant's claimed methods related to PAD are not obvious in light of the claims of the '934 patent, alone or in combination with Moyer *et al.* The additional references cited in the Office Action, Regensteiner *et al.* and Santilli and Santilli, disclose walking impairment and limb ischemia in patients with perfusion disorders and fail to cure the deficiencies of Moyer *et al.* Accordingly, the rejection should be withdrawn.

Paragraph 18.

The Office Action next states that "in its totality US 6440934 teaches the administration of FGF or a sequence identical to SEQ ID NO:2 of the instant application to a peripheral vein within similar dosage range." *See* paragraph 18 of the Office Action. Under obviousness-type double patenting analysis, the claims must be compared, not the disclosures. *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082 (Fed. Cir. 1985), *remanded*, 475 U.S. 809 (1986), *on remand*, 810 F.2d 1561 (Fed. Cir. 1987). Thus, the present rejection's focus upon the "totality" of the '934 patent's teachings is improper, and the rejection should be withdrawn.

Paragraphs 19, 20, and 23.

In the previous amendment, Applicant stated that the administration protocol recited in the presently claimed invention is not taught or suggested by the '934 patent or the Moyer *et al.* reference, as evidenced by the fact that in Moyer *et al.* none of the animal models teach or suggest the claimed method of administration. Specifically, Applicant noted that one could not predict from the claims of the '934 patent the efficacy of dividing the therapeutically effective amount of FGF into two doses, and administering a single one of these two doses into each leg of a PAD patient within a one hour period. Applicant further pointed out that Yang *et al.* (cited by

Moyer *et al.* on page 1435) state that "the route of administration may not require local arterial administration" and, consequently, Yang *et al.* (and consequently Moyer *et al.*) teaches away from administration to each leg for peripheral artery insufficiency.

The Office Action now notes that Moyer *et al.* teaches "a 'bolus dosing protocol'" and takes a position that the route of administration is not critical. *See* paragraphs 19, 20, and 23 of the Office Action. In particular, the Office Action asserts "the statement of Yang *et al.* actually supports the Examiner's position that regardless of where the FGF is administered, it will have a beneficial effect." *See* paragraph 20 of the Office Action. Applicant emphasizes that Yang *et al.* (and, consequently, Moyer *et al.*) teaches away from the methods claimed in the present application. Therefore, there is no motivation to combine Moyer *et al.* with the claimed subject matter of the '934 patent.

Further, to the extent that the Office Action relies upon Yang *et al.* to demonstrate that one of skill in the art would be "*assured* of a therapeutic effect on the patient after FGF administration even if local administration is not practiced," this reliance is misplaced. The quoted passage of Yang *et al.* only *speculates* that "the route of administration *may* not require local arterial administration" (emphasis added). Nothing in this quotation provides an assurance that a therapeutic effect would be observed no matter which protocol is used. Notably, Moyer *et al.* themselves never reached any conclusions regarding the route of administration. Further, Moyer *et al.* reached no certain conclusions regarding the efficacy of FGF in treating PAD. Instead, they only concluded that "[t]his review provides a strong scientific rationale for the use of bFGF as a *potential* therapeutic agent for the treatment of ischaemic stroke and peripheral vascular disease" (emphasis added). Yang *et al.*'s speculative statements quoted in Moyer *et al.*, taken alone or in combination with the '934 patent claims, do not obviate Applicant's claimed invention.

Paragraphs 21 and 22.

In the preceding Office Action, Applicant noted the differences between the claimed subject matter of the '934 claims, which are drawn to methods of treating CAD, and those of the present application, which rely upon a different protocol for treating a different disorder, PAD.

The Office Action now asserts that "Moyer *et al.* teaches the usefulness of FGF in the treatment of several peripheral artery disease models including rats and rabbit models...." In paragraph 22, the Office Action adds Baffour *et al.* (1992) *J. Vascular Surg.*, 16:181-191 and asserts that it would have been obvious "to modify the regiment to maximize the therapeutic effects of FGF" and that "administration was not critical to achieve the beneficial properties of FGF." If the Office Action intends that one of skill in the art would have modified the claimed subject matter of the '934 patent to achieve the presently claimed invention, this has not been established because nothing in the record shows that there was motivation to combine the references of record with the claimed subject matter of the '934 patent or a reasonable chance of success in so doing. As stated above, Moyer *et al.* reviewed the results of several animal model studies and merely reached a conclusion that there was a scientific rationale for exploring the *potential* of FGF in treating peripheral vascular disease. Baffour *et al.*, which teaches use of bFGF in a rabbit model of acute lower limb ischemia, fails to cure the deficiencies of Moyer *et al.* Applicant respectfully submits that use of IA, IM, IV, or SC administration *in accordance with the administration protocol* of the presently claimed invention is not rendered obvious by the combination of Moyer *et al.* and Baffour *et al.* with the subject matter of the '934 patent claims.

Paragraph 24.

The Office Action further states that the '934 patent claims the use of heparin with FGF in a method for treating coronary artery disease in a patient. Nonetheless, heparin co-administration in a dependent claim does not render obvious the method of administration recited in the respective base claim, and the present method of administration is not taught or rendered obvious by this teaching. Furthermore, the properly interpreted claims must be considered as a whole. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1772 (Fed. Cir. 1992). It is error to treat one claim limitation as if it were prior art as the Office Action has done by focusing upon the heparin limitation to the exclusion of the other limitations of the '934 patent claims. In any case, for the reasons stated above, the '934 patent and Moyer *et al.* are insufficient, alone or in combination, to establish that the claims of the present application are obvious.

Paragraphs 25 and 26.

The Office Action again asserts that clinical endpoints were known and that Moyer *et al.* taught that FGF was a promising therapeutic molecule. See the Office Action, paragraphs 25 and 26. However, for the reasons already stated, the '934 patent and Moyer *et al.* are insufficient, alone or in combination, to establish that the claims of the present application are obvious.

In summary, there was no motivation to modify either Moyer *et al.* or the claimed subject matter of the '934 patent, or to combine the teachings of Moyer *et al.* with the subject matter of the '934 claims, to arrive at Applicant's presently claimed invention. Further, even if such motivation were to exist, Moyer *et al.* and the claimed subject matter of the '934 patent do not provide to one of skill in the art a reasonable expectation of success. Finally, PAD and CAD are separate and distinct clinical conditions, with discrete symptoms and treatments. The successful treatment of one does not provide a reasonable expectation of success for treating the other, particularly when different treatment regimens are being used. Accordingly, the '934 claims and Moyer *et al.* fail to teach or suggest the treatment of PAD in the manner set forth in Applicant's claimed invention.

In responding to each of these points, the Office Action has either focused upon specific limitations of each of the '934 claims and cited the limitation against the present claims as if each were prior art or relied upon the teachings of the '934 patent in its "totality." Neither standard is proper. Each of the *claims* of the '934 must be compared to the claims of the present application. Further, the method claims of both the '934 patent and the present application have been analyzed as though they were product claims or product-by-process claims.

For all of these reasons, the present rejection under the doctrine of obviousness-type double patenting should be withdrawn.

CONCLUSION

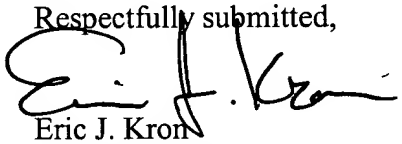
In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under the judicially created the doctrine of obviousness-type double patenting are overcome. The Examiner is respectfully requested to withdraw the

rejections and allow claims 1-82. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of furthering prosecution. The amendments were made in response to the Examiner's suggestion.

Accordingly, in view of the above remarks, it is submitted that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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